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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/768,194	02/02/2004	Douglas Hovey	029318-1001	3657
31049 7590 04/01/2009 Elan Drug Delivery, Inc. c/o Foley & Lardner 3000 K Street, N.W. Suite 500 Washington, DC 20007-5109				
EXAMINER				
HOLT, ANDRIAE M				
ART UNIT		PAPER NUMBER		
1616				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/768,194

**Applicant(s)**

HOVEY ET AL.

**Examiner**

Andriae M. Holt

**Art Unit**

1616

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 15 January 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 17, 19-24, 27-44, 47-61, 64-67 and 69-81 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 17, 19-24, 27-44, 47-61, 64-67 and 69-81 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Andriae M. Holt.

This Office Action is in response to the request for consideration filed January 15, 2009. Claims 17, 19-24, 27-44, 47-61, 64-67, and 69-81 are pending in the application. Claims 17, 19-24, 27-44, 47-61, 64-67, and 69-81 will presently be examined to the extent they read on the elected subject matter of record.

Rejections not reiterated from the previous Office Action are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17, 19-24, 28-44, 47, 49-61, 64-67, 69, and 71-81 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Wiedmann et al. (US 5,747,001) in view of Saidi et al. (US 6,241,969).

***Applicant's Invention***

Applicant claims a sterile filterable dispersion comprising a) an aqueous dispersion medium; b) fluticasone particles and c) at least one surface stabilizer absorbed on the surface of the fluticasone particles. Applicant claims the dispersion is sterilized by filtration through a 0.2  $\mu$ m filter. Applicant claims a method of making a fluticasone composition. Applicant also claims a method of treating a subject in need of either symptomatic or prophylactic treatment with a sterile particulate fluticasone composition.

***Determination of the scope of the content of the prior art  
(MPEP 2141.01)***

Wiedmann et al. teach an aerosol comprising droplets of an aqueous dispersion of nanoparticles, said nanoparticles comprising insoluble beclomethazone particles having a surface modifier on the surface thereof. There is also disclosed a method for making the aerosol and methods for treatment using the aerosol (Abstract). Wiedmann

et al. teach the aerosols of the present invention are particularly useful in the treatment of respiratory related illnesses. Wiedmann et al. teach that beclomethazone is particularly useful in the treatment of seasonal or perennial rhinitis and is also indicated for the relief of the symptoms of seasonal or perennial allergic and non-allergic (vasomotor) rhinitis (col. 2, lines 66-67-col. 3, lines 1-5). Wiedmann et al. teach that suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Wiedmann et al. further teach such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and ionic surfactants. Wiedmann et al. teach tyloxapol is a preferred surface modifier and is a nonionic liquid polymer (col. 4, lines 52-67). Wiedmann et al. teach other specific surface modifiers that can be used in col. 3, lines 29-67-col. 4, lines 1-51). Wiedmann et al. teach examples include methylcellulose, vinyl acetate, polyvinyl pyrrolidone, gelatin, and casein (claims 32-37).

Wiedmann et al. teach the particles can be prepared in a method comprising the steps of dispersing beclomethazone in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the beclomethazone to an effective average particle size of less than about 400 nm (claims 39-41, grinding). Wiedmann et al. teach the particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition (col. 5, lines 65-67-col. 6, lines 1-7). Wiedmann et al. teach the coarse beclomethazone selected can then be added to a liquid medium in which it is essentially insoluble to form a premix. Wiedmann et al. teach the premix can

be used directly by subjecting it to mechanical means to reduce the average particle size in the dispersion to less than 400 nm. Wiedmann et al. teach it is preferred that the premix be used directly when a ball mill is used for attrition. Wiedmann et al. teach that alternatively, the beclomethazone and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation, e.g., a roller mill or a Cowles type mixer, until a homogeneous dispersion is observed in which there are no large agglomerates visible to the naked eye (claim 42, homogenizing). It is preferred that the premix be subjected to such a premilling dispersion step when a recirculating media mill is used for attrition (col. 6, lines 17-40). Wiedmann et al. teach that another method of forming the desired nanoparticle dispersion is by microprecipitation. Wiedmann et al. teach this is a method of preparing stable dispersions of beclomethazone in the presence of a surface modifying and colloid stability enhancing surface active agent free of trace of any toxic solvents or solubilized heavy metal impurities by the following procedural steps: 1) Dissolving the beclomethazone in aqueous base with stirring, 2) Adding above #1 formulation with stirring to a surface active surfactant (or surface modifiers) solution to form a clear solution, and, 3) Neutralizing above formulation #2 with stirring with an appropriate acid solution. Wiedmann et al. teach the procedure can be followed by: 4) Removal of formed salt by dialysis or diafiltration and 5) Concentration of dispersion by conventional means. Wiedmann et al. teach this microprecipitation process produces dispersion of beclomethazone with Z-average particle diameter less than 400 nm (col. 9, lines 6-26). Wiedmann et al. teach an advantage of the microprecipitation is that unlike milled dispersion, the final product is

free of heavy metal contaminants arising from the milling media that must be removed due to their toxicity before product is formulated (col. 9, lines 57-60). Wiedmann et al. teach in preferred embodiments, the effective average particle size is less than about 300 nm and more preferably less than about 250 nm. Wiedmann et al. teach in some embodiments, an effective average particle size of less than about 100 nm has been achieved. Wiedmann et al. teach it is preferred that at least 95% and, more preferably, at least 99% of the particles have a particle size less than the effective average, e.g., 400 nm. Wiedmann et al. further teach that in some embodiments, essentially all of the particles have a size less than 250 nm (col. 10, lines 28-39).

***Ascertainment of the difference between the prior art and the claims  
(MPEP 2141.02)***

Wiedmann et al. do not teach fluticasone particles or sterile filtration. It is for this reason Saidi et al. is added as a secondary reference.

Saidi et al. teach compositions containing corticosteroid compounds as active agents for the treatment of ailments and diseases of the respiratory tract, particularly the lungs, by way of nasal and pulmonary administration (Abstract). Saidi et al. teach the corticosteroid compositions of the present invention are preferably formulated with ethoxylated derivatives of vitamin E as the high-HLB surfactant component. An example of a preferred high-HLB surfactant from this class of surfactants is tocopheryl polyethylene glycol 1000 succinate ("TPGS") (col. 5, lines 40-42). Saidi et al. teach the particularly preferred are compounds include beclomethasone dipropionate, budesonide, and fluticasone propionate (col. 6, lines 27-30) (fluticasone). Saidi et al.

teach in example 1, col. 9, lines 65-67-col. 10, lines 1-16, the corticosteroid compositions were sterilized by passing them through a 0.22 micron sterile filter. Saidi et al. teach that for the treatment of bronchial constriction, the diluted corticosteroid composition is prepared as described above (sterile filtration and .2  $\mu$ m filter). Saidi et al. teach the corticosteroid for such treatment is preferably beclomethasone dipropionate, betamethasone, budesonide, dexamethasone, flunisolide, fluticasone propionate, or triamcinolone acetonide (col. 9, lines 47-53).

***Finding of prima facie obviousness  
Rationale and Motivation (MPEP 2142-2143)***

It would have been obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Wiedmann et al. and Saidi et al. and use fluticasone in the formulation. Wiedmann et al. teach aqueous dispersions of nanoparticles comprising beclomethasone particles that have a surface modifier on the surface used in the treatment of respiratory related illnesses. One skilled in the art at the time the invention was made would have been motivated to use fluticasone in the formulation because Saidi teach that fluticasone and beclomethasone are preferred compounds in the treatment of ailments and diseases of the respiratory system. Therefore, one skilled in the art at the time of invention would have been motivated to use fluticasone with a reasonable expectation of success as fluticasone and belcomethasone are functional equivalent glucocorticosteroids in the treatment of respiratory illnesses.

It would also have been obvious to one of ordinary skill in the art that the time the invention was made to use the sterile filtration technique as taught by Saidi et al. in the



formulations and process of Wiedmann et al. since Wiedmann et al. teach filtration of nanoparticles of beclomethasone and tyloxapol, the preferred surface stabilizer of the instant application. One skilled in the art at the time the invention was made would have been motivated to implement sterile filtration of Saidi et al. instead of simple filtration of Wiedmann et al. because sterilization of formulations is beneficial to recipients.

Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited reference.

Claims 17, 19-24, 27-44, 47-61, 64-67, and 69-81 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Wood et al. (WO 96/25918) in view of Saidi et al. (US 6,241,969) in further view of Biggadike et al. (US 2003/0073676).

#### ***Applicant's Invention***

Applicant claims a sterile filterable dispersion comprising a) an aqueous dispersion medium; b) fluticasone particles and c) at least one surface stabilizer absorbed on the surface of the fluticasone particles. Applicant claims the dispersion is sterilized by filtration through a 0.2  $\mu$ m filter. Applicant claims a method of making a fluticasone composition. Applicant also claims a method of treating a subject in need of either symptomatic or prophylactic treatment with a sterile particulate fluticasone composition.

***Determination of the scope of the content of the prior art  
(MPEP 2141.01)***

Wood et al. teach an aerosol comprising droplets of an aqueous dispersion of nanoparticles wherein the nanoparticles comprise insoluble therapeutic or diagnostic agent particles having a surface modifier on the surface (page 2, lines 25-28). Wood et al. further teach a method of treating a mammal comprising the steps of forming an aerosol of an aqueous dispersion of nanoparticles, wherein the nanoparticles comprise insoluble therapeutic agent particles having a surface modifier on the surface and administering the aerosol to the respiratory system of the mammal (page 2, lines 35-36- page 3, lines 1-5). Wood et al. teach the aerosols are useful in the treatment of respiratory related illnesses such as asthma, emphysema, respiratory distress syndrome, chronic bronchitis, cystic fibrosis, and AIDS related pneumonia (conditions and method of treating). Wood et al. teach suitable therapeutic agents can be elected from a variety of known classes including anti-inflammatory agents and corticosteroids (page 4, lines 26-36). Wood et al. teach suitable surface modifiers can be selected from known organic and inorganic pharmaceutical excipients. Wood et al. teach the excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Wood et al. teach preferred surface modifiers include nonionic and ionic surfactants (page 6, lines 2-5). Wood et al. teach representative examples of surface modifiers include casein, lecithin, gum acacia, polyethylene glycols, PVP (page 6, lines 6-21). Wood et al. teach preferred surface modifiers include tyloxapol (tyloxapol) (page 6, lines 22-36). Wood et al. teach that two or more surface modifiers can be used in combination (page 7, lines 33-34) (at least 2 surface stabilizers).

Wood et al. teach the particles can be prepared in a method comprising the steps of dispersing a therapeutic or diagnostic agent in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the therapeutic agent to an effective average particle size of less than about 400 nm. Wood et al. teach the particles can be reduced in size in the presence of a surface modifier (page 9, lines 30-32-page 10, lines 1-5) (method of making, grinding). Wood et al. teach the surface modifier is present in an amount of 0.1-90%, preferably 20-60% by weight based on the total weight of the dry particle (page 17, lines 10-11) (weight ratios). Example 1 teaches the preparation and use of beclomethasone nanoparticles (page 18, lines 17-36).

***Ascertainment of the difference between the prior art and the claims  
(MPEP 2141.02)***

Wood et al. do not teach fluticasone particles, sterile filtration. It is for this reason Saidi et al. and Biggadike et al. are added as a secondary references.

The teachings of Saidi et al. are incorporated herein by reference and are therefore applied in the instant rejection as discussed above.

Biggadike et al. teach a pharmaceutical formulation comprising an aqueous carrier liquid having dissolved therein an ester of fluticasone or a solvate as medicament and a solubilizing agent for assisting the solubilization of the medicament in the aqueous carrier liquid. Biggadike et al. teach that fluticasone esters are quite insoluble in water (page 2, paragraph 15). Biggadike et al. teach that the solubility of fluticasone esters can be increased by dissolution in the aqueous carrier liquid of a hydroxyl containing organic co-solvating agent or of phosphatidyl choline (page 2,

paragraph 16). Biggadike et al. further teach the preferred surfactant to be used as the solubilizing agent is tyloxapol (page 2, paragraph 21). Biggadike et al. teach that the formulations of the inventions may be employed for rectal, aural, otic, topical or parenteral administration or administration by inhalation for the treatment of other local inflammatory conditions such as dermatitis, asthma, and COPD (page 4, paragraph 56) (conditions and methods of administration).

***Finding of prima facie obviousness  
Rationale and Motivation (MPEP 2142-2143)***

It would have been obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Wood et al., Saidi et al., and Biggadike et al. and use fluticasone in the formulation. Wood et al. teach the preparation, method of making and method of using aqueous dispersion of nanoparticles wherein the nanoparticles comprise insoluble therapeutic or diagnostic agent particles having a surface modifier on the surface. Wood et al. specifically teach that preferred examples of agents that can be used in the preparation include anti-inflammatory and corticosteroids, of which drug classes fluticasone belongs. In addition, the working example uses beclomethasone in the preparation of the nanoparticles. One skilled in the art at the time the invention was made would have been motivated to use fluticasone in the formulation because Saidi teach that fluticasone and beclomethasone are preferred compounds in the treatment of ailments and diseases of the respiratory system. In addition, Biggadike et al. teach that the preferred surface stabilizer, tyloxapol, is a preferred surfactant used to solubilize fluticasone and fluticasone esters. Therefore, one skilled in the art at the time of

invention would have been motivated to use fluticasone in the formulation with a reasonable expectation of success as fluticasone and beclomethasone are functional equivalent glucocorticosteroids in the treatment of respiratory illnesses and fluticasone is a member of two of the preferred drug classes that can be used in making the aerosol.

It would also have been obvious to one of ordinary skill in the art that the time the invention was made to use the sterile filtration technique as taught by Saidi et al. in the formulations and process of Wood et al. since Wood et al. teach filtration of nanoparticles of beclomethasone and tyloxapol, the preferred surface stabilizer of the instant application. One skilled in the art at the time the invention was made would have been motivated to implement sterile filtration of Saidi et al. instead of simple filtration of Wood et al. because sterilization of formulations is beneficial to recipients.

Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited reference.

None of the claims are allowed.

### ***Conclusion***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Bhatarah et al. (US 2005/0222108).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andriae M. Holt whose telephone number is (571)272-9328. The examiner can normally be reached on 7:00 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richter Johann can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Andriae M. Holt  
Patent Examiner  
Art Unit 1616

/John Pak/  
Primary Examiner, Art Unit 1616